BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

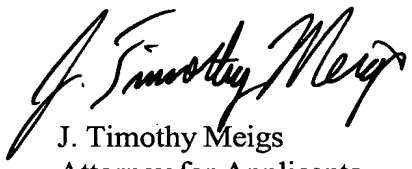
IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Also in response to the Notice to File Missing Parts, Applicants have submitted substitute drawings in compliance with 37 CFR 1.84. A number of descriptive legends have been deleted from the substitute drawings and relocated to the specification. Accordingly, a number of the figure descriptions in the specification have been amended. Figure 26B and the description thereof in the specification have also been amended to add a reference to SEQ ID NO:98. No new matter has been added, as the subject matter added to the figure descriptions was in the originally filed drawings themselves.

The Examiner is respectfully requested to enter the above amendments before calculation of the claim fee and commencement of substantive examination. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call Applicants' undersigned attorney.

Respectfully submitted,



J. Timothy Meigs
Attorney for Applicants
Registration No. 38,241

Genetic Therapy, Inc.
9 W. Watkins Mill Road
Gaithersburg, MD 20878
Telephone: 301-258-4715

July 29, 2002

MARKED-UP VERSION SHOWING CHANGES MADE

The enclosed paper Sequence Listing, pages 1-36, has been added to the specification.

On page 2, the description of Figure 3 has been amended as follows:

-- Figures 3A-3C: Sequence of Ar6pAE2fF from left and right ends of viral DNA. Regions of Ar6pAE2fF confirmed by DNA sequencing. [Panel A.] Figures 3A-3B: Regions in first 1802 nucleotides are the inverted terminal repeat (ITR) (nucleotides 1-103), poly-adenylation signal (nucleotides 116-261), a human E2F-1 promoter (nucleotides 283-555), E1A gene (nucleotides 574-1647) and a portion of the E1b gene (nucleotides 1648-1802) are indicated (SEQ ID NO:3). [Panel B.] Figure 3C: Regions in the last 531 nucleotides are the PacI restriction site (nucleotides 33967-33974) (underlined), the packaging signal (nucleotides 34020-34217 and the ITR (34310-34412). --

On page 2, the description of Figure 4 has been amended as follows:

-- Figure 4: Sequence of Ar6F from left end of viral DNA [(SEQ ID NO:4)] (SEQ ID NO:5). The first 660 nucleotides at the left end of Ar6F. The ITR (nucleotides 1-103), a multiple cloning site (MCS) (nucleotides 104-134) and a portion of the E1A gene (nucleotides 135-660) are shown. –

On page 2, the description of Figure 5 has been amended as follows:

-- Figure 5: Sequence of Ar6pAF from left end of viral DNA (SEQ ID NO:6). The first 660 nucleotides at the left end of Ar6pAF. The ITR (nucleotides 1-103), the SV40 early polyA signal (nucleotides 104-134) and a portion of the E1A gene (nucleotides298-660) are shown. --

On page 3, the description of Figure 10 has been amended as follows:

-- Figure 10: Survival of tumor-bearing animals after intratumoral injections of [Ar6pAE2fF] vectors to H460 tumors. Survival of tumor bearing animals after treatment with Ar6pAE2fF. Animals were observed until study day 32. Numbers of animals in each treatment group were as follows: HBSS, n = 13; Ar6pAE2fF at $5x10^8$, n = 13; $5x10^9$, n = 13;

and $5x10^{10}$ particles/dose/day, n=12; and Addl327 at $5x10^{10}$ particles/dose/day, n =12. The survival of animals was analyzed by the Mantel-Haenszel logrank test. --

On page 3, the description of Figure 12 has been amended as follows:

-- Figure 12: Survival of tumor-bearing animals after intratumoral injections of [Ar6pAE2fF] vector to Hep3B tumors. Survival of tumor bearing animals after treatment with Ar6pAE2fF. Animals were observed until study day 32. Numbers of animals in each treatment group were as follows: HBSS, n = 11; Ar6pAE2fF at $5x10^{8}$, n = 11; $5x10^{9}$, n = 11; and $5x10^{10}$ particles/dose/day, n=10; and Addl327 at $5x10^{10}$ particles/dose/day, n =11. The survival of animals was analyzed by the Mantel-Haenszel logrank test. --

On page 5, the description of Figure 25 has been amended as follows:

-- Figure 25: Schematic diagram of PCR and overlap PCR for [□gp19] Δgp19 donor plasmids The mGM-CSF or hGM-CSF cDNA was inserted into the E3 region replacing the E3-gp19 open reading frame (ORF) using two steps of PCR amplification. In the first step, 3 individual PCR amplifications were carried out using 3 pairs of primers and corresponding DNA templates. In the second step, the 3 DNA fragments generated in first step were mixed as the template DNA for the overlap PCR amplification using primer 1 and primer 6 as primers. The overlap PCR product was then digested with BsiWI/NotI and used to replace the BsiWI/NotI region of adenoviral E3 containing the E3-gp19 open reading frame. --

On page 5, the description of Figure 26 has been amended as follows:

-- Figures 26A-26B: Schematic Diagram of Δgp19 Vectors. Figure 26A: Sequence of native E3 region (SEQ ID NO:9 and SEQ ID NO:13). Figure 26B: Sequence Comparison of Δgp19 vectors at the junction between E3-6.7 and GMCSF (SEQ ID NO:98; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13). --

On page 10, the description of Figure 49 has been amended as follows:

-- Figure 49: E4 expression is dependent on the hTERT promoter. Adenoviral E4 expression measured by semi-quantitative RT-PCR. The E4 region is encoded on the opposite strand in the viral genome. Total RNA was isolated from Hep3B cells 24 hours after infection

with 10 ppc of Ar17pAE2fFTrtex. Depicted is a schematic diagram of the right end of the Ar17pAE2fFTrtex viral genome with relative positions of primers used in RT-PCR reactions along with the approximate size of the products. PCR 2.f paired with PCR 3.r or PCR 4.r were designed to detect all E4 transcripts. PCR 2.f paired with PCR 5.r was used to detect transcripts that initiated from any cryptic start sites upstream of the E4 region. +1, indicates the approximate position of transcriptional initiation site of the native hTERT promoter. --

On page 10, the description of Figure 51 has been amended as follows:

-- Figure 51: Efficacy of Ar17pAE2fFTrtex in Hep3B model. Tumors were established by injecting 1 x 10^7 Hep3B cells subcutaneously into the right flank of 6-8 week old female nude mice (Harlan). Two weeks after implantation, mice with tumors ranging from 91.6 – 218.5 mm^3 were selected and randomly distributed into groups (n=17-18). Each mouse was weighed prior to intravenous injection. The control groups received HBSS or Addl312 at 4.5 x 10^{12} vp/kg (n=18). Ar17pAE2fFTrtex treatment groups received 1.5x10^{12} (n=18), 3.0x10^{12} (n=17), or 4.5x10^{12} (n=18) vp/kg. All dose volumes were 10 ml/kg. Groups means + SEM are represented. *, $p < 0.05$ *vs.* HBSS controls (Dunnett test). --

On page 11, the description of Figure 53 has been amended as follows:

-- Figure 53: Body weight changes. Group mean body weights are shown following a single intravenous injection of the indicated test article. The number of animals evaluated at each scheduled data collection time point was 18-33, except for SD29 when n = 9-22. Vector doses were adjusted on the basis of individual animal body weight on the day of dosing. Lo Dose: 1.5 x 10^{12} vp/kg; Mid Dose: 3.0 x 10^{12} vp/kg; Hi Dose: 4.5 x 10^{12} vp/kg. Group means + SD are represented, with no statistically significant differences between groups. --

On page 11, the description of Figure 54 has been amended as follows:

-- Figure 54: Efficacy of Ar17pAE2fFTrtex in Hep3B model. Comparison of *in vivo* growth of Hep3B tumors after a single iv injection of Ar17pAE2fFTrtex at 3x10^{12} (n=16) or 4.5x10^{12} (n=16) particles/kg. Control groups were injected with HBSS (n=16) or Addl312 (n=16) at 4.5x10^{12} particles/kg. Data is expressed as mean tumor volume + SE. (*$p < 0.05$)

For both Ar17pAE2fFTrtex treated groups compared to HBSS treated controls using one-way ANOVA with Student-Newman-Keuls test for multiple comparison. --

On pages 11-12, the description of Figure 57 has been amended as follows:

-- Figure 57: Dose-dependent anti-tumor efficacy. Tumors were established by injecting 1 x 10^7 Hep3B cells subcutaneously into the right flank of 6-8 week old female nude mice (Harlan). Two weeks after implantation, mice with tumors ranging from 90 – 215 mm^3 were selected and randomly distributed into groups (n=12/group). Each mouse was weighed prior to intravenous injection. The control mice received HBSS. Ar17pAE2fFTrtex treatment groups received $3x10^{11}$ (n=12), $6x10^{11}$ (n=12), $1x10^{12}$ (n=12), or $3x10^{12}$ (n=12) vp/kg. All dose volumes were 10 ml/kg. Groups means (+SEM) are represented. *, $p < 0.05$ vs. HBSS controls (Dunnett's method). --

On page 12, the description of Figure 58 has been amended as follows:

-- Figure 58: Individual tumor volumes following intravenous administration of Ar17pAE2fFTrtex for study days 3 through 22 are presented. All dose volumes were 10 ml/kg. A) The control group treated with HBSS. Treatment groups received Ar17pAE2fFTrtex at B) $3x10^{11}$ vp/kg, C) $6x10^{11}$ vp/kg, D) $1x10^{12}$, or E) $3x10^{12}$ vp/kg. (n=12 / group). --

On page 12, the description of Figure 62 has been amended as follows:

-- Figure 62: Effect on body weight in SCID mice. The mean body weight change as a percent of the SD1 body weight +st dev was followed for a cohort of five mice in each treatment group. Animals were injected with a single intravenous dose of the indicated vectors on SD1. *, $p < 0.05$ vs. HBSS (one-way ANOVA). --

On page 37, the last 3 lines have been amended as follows:

-- Hexon Forward primer: 5'-CTTCGATGATGCCGCAGTG-3' [(SEQ ID NO:25)] (SEQ ID NO:95)

Hexon Reverse primer: 3'-GGGCTCAGGTACTCCGAGG-3' [(SEQ ID NO:26)] (SEQ ID NO:96)

Hexon Probe: 5'-FAM-TTACATGCACATCTCGGGCCAGGAC-TAMRA-3' [(SEQ ID NO:27)] (SEQ ID NO:97) --